ENDOGLIN POLYPEPTIDES AND USES THEREOF

RELATED APPLICATIONS

[0001] This application claims the benefit of the filing date under 35 U.S.C. § 119(e) to U.S. Provisional Patent Application Ser. No. 61/477,585, filed Apr. 20, 2011, entitled "Endoglin Polypeptides And Uses Thereof," the entire contents of which are incorporated herein by reference.

BACKGROUND

[0002] Angiogenesis, the process of forming new blood vessels, is critical in many normal and abnormal physiological states. Under normal physiological conditions, humans and animals undergo angiogenesis in specific and restricted situations. For example, angiogenesis is normally observed in wound healing, fetal and embryonic development and formation of the corpus luteum, endometrium and placenta.

[0003] Undesirable or inappropriately regulated angiogenesis occurs in many disorders, in which abnormal endothelial growth may cause or participate in the pathological process. For example, angiogenesis participates in the growth of many tumors. Deregulated angiogenesis has been implicated in pathological processes such as rheumatoid arthritis, retinopathies, hemangiomas, and psoriasis. The diverse pathological disease states in which unregulated angiogenesis is present have been categorized as angiogenesis-associated diseases.

[0004] Both controlled and uncontrolled angiogenesis are thought to proceed in a similar manner. Capillary blood vessels are composed primarily of endothelial cells and pericytes, surrounded by a basement membrane. Angiogenesis begins with the erosion of the basement membrane by enzymes released by endothelial cells and leukocytes. The endothelial cells, which line the lumen of blood vessels, then protrude through the basement membrane. Angiogenic factors induce the endothelial cells to migrate through the eroded basement membrane. The migrating cells form a "sprout" protruding from the parent blood vessel, where the endothelial cells undergo mitosis and proliferate. Endothelial sprouts merge with each other to form capillary loops, creating the new blood vessel.

[0005] Agents that inhibit angiogenesis have proven to be effective in treating a variety of disorders. Avastin™ (bevacizumab), a monoclonal antibody that binds to vascular endothelial growth factor (VEGF), is used in the treatment of a variety of cancers. Macugen™, an aptamer that binds to VEGF has proven to be effective in the treatment of neovascular (wet) age-related macular degeneration. Antagonists of the SDF/CXCR4 signaling pathway inhibit tumor neovascularization and are effective against cancer in mouse models (Guleng et al. Cancer Res. 2005 Jul. 1; 65(13):5864-71). A variety of so-called multitargeted tyrosine kinase inhibitors, including vandetanib, sunitinib, axitinib, sorafenib, vatalanib, and pazopanib are used as anti-angiogenic agents in the treatment of various tumor types. Thalidomide and related compounds (including pomalidomide and lenalidomide) have shown beneficial effects in the treatment of cancer, and although the molecular mechanism of action is not clear, the inhibition of angiogenesis appears to be an important component of the anti-tumor effect (see, e.g., Dredge et al. Microvasc Res. 2005 January; 69(1-2): 56-63). Although many anti-angiogenic agents have an effect on angiogenesis regardless of the tissue that is affected, other angiogenic agents may tend to have a tissue-selective effect.

[0006] It is desirable to have additional compositions and methods for inhibiting angiogenesis. These include methods and compositions which can inhibit the unwanted growth of blood vessels, either generally or in certain tissues and/or disease states.

SUMMARY

[0007] In part, the present disclosure provides endoglin (ENG) polypeptides and the use of such endoglin polypeptides as selective antagonists for BMP9 and/or BMP10. As described herein, polypeptides comprising part or all of the endoglin extracellular domain (ECD) bind to BMP9 and BMP10 while not exhibiting substantial binding to other members of the TGF-beta superfamily. This disclosure demonstrates that polypeptides comprising part or all of the endoglin ECD are effective antagonists of BMP9 and BMP10 signaling and act to inhibit angiogenesis and tumor growth in vivo. Thus, in certain aspects, the disclosure provides endoglin polypeptides as antagonists of BMP9 and/or BMP10 for use in inhibiting angiogenesis as well as other disorders associated with BMP9 or BMP10 described herein.

[0008] In certain aspects, the disclosure provides polypeptides comprising a truncated extracellular domain of endoglin for use in inhibiting angiogenesis and treating other BMP9 or BMP10-associated disorders. While not wishing to be bound to any particular mechanism of action, it is expected that such polypeptides act by binding to BMP9 and/or BMP10 and inhibiting the ability of these ligands to form signaling complexes with receptors such as ALK1, ALK2, ActRIIA, ActRIIB and BMPRII. In certain embodiments, an endoglin polypeptide comprises, consists of, or consists essentially of, an amino acid sequence that is at least 70%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to the sequence of amino acids 42-333, 26-346, 26-359 or 26-378 of the human endoglin sequence of SEQ ID NO:1. An endoglin polypeptide may comprise, consist of, or consist essentially of an amino acid sequence that is at least 70%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to the sequence of amino acids beginning at any of positions 26-42 of SEQ ID NO:1 and ending at any of positions 333-378 of the human endoglin sequence of SEQ ID NO:1. An endoglin polypeptide may comprise, consist of, or consist essentially of, a polypeptide encoded by a nucleic acid that hybridizes under less stringent, stringent or highly stringent conditions to a complement of a nucleotide sequence selected from a group consisting of: nucleotides 537-1412 of SEQ ID NO: 2, nucleotides 121-1035 of SEQ ID NO: 30, nucleotides 121-1074 of SEQ ID NO: 26, nucleotides 121-1131 of SEQ ID NO: 24, nucleotides 73-1035 of SEQ ID NO: 30, nucleotides 73-1074 of SEQ ID NO: 26, and nucleotides 73-1131 of SEQ ID NO: 24. In each of the foregoing, an endoglin polypeptide may be selected such that it does not include a full-length endoglin ECD (e.g., the endoglin polypeptide may be chosen so as to not include the sequence of amino acids 379-430 of SEQ ID NO:1, or a portion thereof or any additional portion of a unique sequence of SEQ ID NO:1). An endoglin polypeptide may be used as a monomeric protein or in a dimerized form. An endoglin polypeptide may also be fused to a second polypeptide portion to provide improved properties, such as